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# Increasing Undergraduate Student-Driven Engagement with Biochemical Structures Using Visual Molecular Dynamics (VMD) and Protein Molecular Modeling with Real-World Applications in Biochemistry Class

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**ABSTRACT**

Having a deeper understanding of molecules in their structural forms allows students to grasp biochemical and general chemical concepts in a more profound manner. Through the use of visualization software, we have shown that students gain confidence and insight into the chemical workings of molecular structure and can then utilize this knowledge in its applications to societal health-related issues. In this research, we introduced students in a biochemistry class to visual molecular dynamics software and had them complete several activities. The final project consisted of three parts, including data gathering, team presentations and pitches with peer review, and a final persuasive report Each of these advanced student mastery of the molecular biochemical details while mastering a skill-set that allowed them to think creatively and apply this knowledge to a pertinent world-problem. Overwhelmingly, we found that student interest in the subject, as well as performance and confidence increased across the use of molecular visualization in the classroom. Additionally, upon close inspection, we found that such student-centered work benefitted historically marginalized students. Overall, students who can connect with course materials and embrace real-world, hands-on applications are increasing societal scientific literacy which can trickle down across decision-making and public health.

**KEYWORDS**

Biochemistry; Molecular visualization; Molecular modeling; Student projects; Student engagement; Inclusive pedagogy; Student-Centered pedagogy; Active learning

## Introduction

Understanding applications of science plays a role in individual and community needs, and the ability to make sense of science helps a society thrive. Students at the college level are at a unique vantage point where access to science can be coupled to the process of familiarizing themselves with science as a process, a product, and a repository of knowledge that aids in decision-making, public health, the environment and many other aspects of human life (Feinstein et al, 2013; National Academies, 2016). Enhancing science literacy at the student level is an important goal for educators who hope to influence the next generation of unique, global citizens. Embracing the ever-changing nature of scientific knowledge leads to individuals who can use this knowledge, contribute to it, apply it or even, simply, recognize and appreciate it. As science educators set to this task, we design our classes to maximize student engagement, participation, interest and understanding, but are often stymied by how to best do this while also creating content and covering core materials.

Visualizing and analyzing protein structures is a cornerstone of biochemical education. Proteins have a vast array of biological functions that include structural, mechanistic, and catalytic roles, making them one of the most important biological molecules. The connection between structure and function, the molecular components and the macroscopic job they have, is often reiterated through the curriculum of biochemistry classes. However, to fully grasp this connection students often need to see or experience the way a protein is structured to properly understand its behavior. Software programs like visual molecular dynamics (VMD), which can be used to obtain, visualize, and analyze protein structures, aid in imparting this concept to students (Humphrey et al., 1996). By training students to view and manipulate the intricacies of the molecular world through VMD, they get a unique hands-on experience that leads to clarity and better understanding of the structure and function connection.

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Students often approach new science classes outside of their direct expertise or prior exposure with hesitancy or a negative attitude regarding the difficulty of the subject matter. Linking materials from class to actual, natural phenomena that can influence student understanding and decision-making processes in the "real world" can positively impact student outcomes (Dauer et al., 2021, Marx & Knouse, 2006). Such real world applications can spark student interest, creativity and inspiration in science, and provide a unique path for students to learn science. Having biochemistry students use VMD to probe protein characteristics, interactions, and distances between specific amino acid residues within an interface is an excellent way to give them hands-on experience with molecular structure. By investigating the types of bonds made within these interactions, students can then apply their obtained skills and study a protein-protein interaction involved in pertinent diseases. When students are asked to synergize their background knowledge of protein secondary structure (acquired from the biochemistry course itself) with the techniques from molecular modeling, they are given the space for creativity and agency to work on a pertinent, real-world problem. This overall process increases student interest and engagement with the materials, as they become aware of how the topics and skills they are learning come together for a larger purpose.

We adapted this practice for use in our junior/senior level undergraduate biochemistry course for chemistry majors. As the course is part of our American Chemical Society (ACS) certified curriculum, all chemistry majors graduating with an ACS certified bachelor of science degree are required to take the course. Students come to the course with varying levels of readiness; approximately half have had some form of college-level biology (including advanced placement high school classes, classes at another institution, or biology courses at our institution), whereas the other half may not have seen any biology-related courses since their first year of high school, six or seven (or more) years prior. In this study, we followed student perceptions of protein structure in biochemistry, as well as student outcomes in successful implementation of structure-related details in their studies of proteins, as a result of VMD training. We assessed student insights and ability to apply their biochemical knowledge and VMD training to examine the protein-protein interaction between the SARS-Coronavirus (CoV)-2 spike receptor-binding domain and the Angiotensin Converting Enzyme (ACE)2 receptor; the interaction that facilitates the COVID-19 infection of the current pandemic (Lan et al., 2020). The overall objectives of the tutorial and project, together, were to have students assimilate knowledge about three dimensional protein structure and folding, use data accumulated using the VMD software, and apply this to understand the interaction leading to SARS-CoV-2 infection. To build competency, students gathered VMD-generated information for the development of a peptide-based inhibitor, pitched their design work to other teams for peer-review, and wrote a final, persuasive, proposal meant for a "non-specialist." One of our interests in administering this type of scaffolded assignment was tracking how student comfort and mastery of basic biochemistry concepts was implied by their work on the project. In addition, we anticipated our direct observation of student engagement and a more clear tie-in to biochemistry as a whole, as a result of the project.

Coupling biochemical skill building with real-world applications with medical importance, the students immersed themselves in biochemistry in a novel way. Having students use VMD training to analyze this particular protein interaction provided a unique approach to teaching students about proteins and disease. Immediately tapping into a skill set and applying it to a topic that garnered student interest was purposeful to aid in engagement and biochemical understanding. This hands-on approach was meant to increase student visualization skills, to aid in viewing biological molecules, which is an essential part of learning biochemistry. In addition, by using a topic that is medically relevant, the project aimed to support student scientific literacy, which, in turn, helps students make informed decisions of societal impact.

VMD can be brought to other classes and the ability to dissect the structures and dynamics of molecules adds to a toolbox students can apply in other classes such as environmental chemistry, inorganic and organic chemistry (e.g. designing environmentally friendly catalysts or new chemical tools). Therefore, we also provide some context about our department's efforts to integrate computation across the curriculum as part of wider transformation efforts. Such classroom experiences can potentially lead to retention in the major, improved interest in the biochemical field, and broad recognition of the importance of science in greater society.

## Objectives and Methods

### *Overall Goals*

The project described here draws in part on a School of Science-wide initiative to encourage faculty to

experiment with incorporating student-centered, active learning pedagogies shown to support all students, but are especially beneficial for those from minoritized groups (Ross, 2016). The Chemistry department has conducted multiple successful experiments, including a full transformation of the multi-section General Chemistry I and incorporating inclusive, active-learning strategies in Organic Chemistry and elective courses. (Chan, et al., 2020). The biochemistry course project contained elements of course-based research and made efforts to expand scientific literacy through a connection to the current global pandemic. Specifically, students prepared for using VMD (Humphreys et al., 1996) by first training with a tutorial designed to introduce them to molecular visualization, with the aim of earning proficiency with the types of manipulations of the program they would need. After this, students applied the techniques from the tutorial to study the interaction between the spike protein receptor binding domain from the SARS-Coronavirus-2 (the virus responsible for COVID-19) and its cellular receptor (Angiotensin Converting Enzyme 2 (ACE2)). The overarching goal of the project was for them to use VMD to probe new questions, come up with solutions and draw conclusions. These are skills we wish our students to gain in any science laboratory regardless of topic or mode of instruction, therefore implementation here was in line with the broader course goals.

The explicit goals of the project itself were three-part, and students accomplished this by working in teams. After training with the tutorial, students *first* explored the SARS-CoV-2 interaction with ACE2 using their VMD skills, including analysis of the distances and identity of amino acids, as well as plans for inhibitor design. *Second*, they creative a persuasive pitch for another team, followed by peer review in workshop format, to test their science-communication skills as well as get feedback. *Third*, they summarized their work in a written proposal meant for a general, science-educated audience using the figures they generated in VMD to illustrate their points and adapting feedback from their peers. At the end of the course, students were surveyed anonymously to reflect on their perceptions of learning biochemistry in regards to the project and how it fit into the entire biochemistry curriculum. A flowchart summarizing the workflow as well as the actions and goals can be seen in Figure 1.

## Methodology and Reasoning

### *Step 1: Tutorial*

In order to prepare students for using VMD (Humphreys et al., 1996) in their project, a tutorial was designed to introduce them to molecular visualization. Since this was not a full course on molecular visualization, the tutorial was designed to help students develop specific skills relevant to the exercises they would be performing in class, but this was balanced with some background information so that the use of the tool was not entirely as a "black box." The first element of the tutorial was to introduce students to the use of the Protein Data Bank (Berman et al., 2000), since students would download a PDB file and load that into VMD for visualization. Students were provided with an overview of the different information available on a protein PDB entry page, and also the contents of a PDB file. In particular, students viewed the contents of a PDB file using a text editor and were shown how to interpret the columns of the file (e.g., amino acid identity, atom name, atom coordinates, etc.) which made the use of VMD more transparent. After learning to download the PDB file from the data bank, students were able to log onto the TCNJ High Performance Cluster, the Electronic Laboratory for Science and Analysis (ELSA) through the Open OnDemand (Hudak et al., 2018) interface. This interface allows students to begin a VMD session

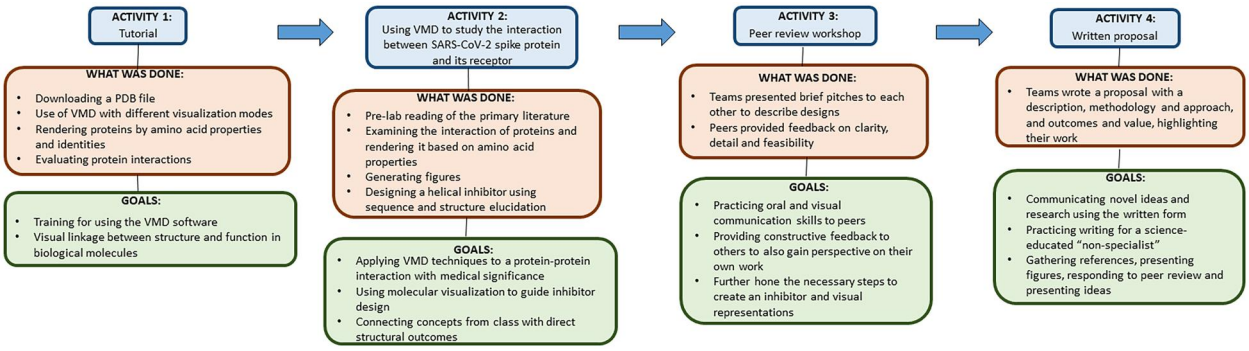


**Figure 1.** Flow chart describing the order of the activities, what was accomplished and the goals of each activity for the VMD project.

on ELSA and run it through their web browser, therefore making the software highly accessible since it does not require significant resources on their local machine. Students were then shown how to load the PDB file in VMD and to change visualization modes of the protein (e.g., to display the protein as a ball-and-stick model, space-filling spheres, or in a cartoon representation as often seen in biochemistry textbooks). Students were also shown how to change coloring schemes within VMD, and in particular how to color the amino acids by properties such as polarity or charge. Other features that were described to students included how to determine amino acid identity through the VMD interface, how to measure distances between atoms in the protein structure, and how to use the VMD Sequence Viewer to display the secondary structure of the protein. By synthesizing information about these properties (e.g., polarity, amino acid identity, interatomic distance), students were able to evaluate the type of interaction that the atoms might be making (e.g., H-bond, salt bridge, or other nonspecific polar/non-polar interactions). The whole guided tutorial took approximately an hour and a half to complete, and presented all of the topics necessary for students to complete the subsequent assignment.

### *Step 2: Applying VMD Training to Examine the SARS-CoV-2 Spike Protein Receptor Binding Domain Interaction with ACE2*

At the start of the project, as a pre-lab assignment, students were asked to read a journal article which describes the elucidation of the SARS-CoV-2 viral protein bound to the human cellular receptor (Lan et al, 2020). To guide the students in gleaning the most important information, we had them read the relevant portions that discussed topics they were already familiar with from class: hydrogen bonding amino acids and secondary structural motifs (mainly helices).

In the first lab session to work on the project, students downloaded the PDB file from the Protein Data Bank and began rendering the complex using VMD. They were provided the criteria and questions shown in Table 1 as "Things to Consider" to help organize their work and to direct their use of the software. As they began to map helical regions they were tasked to think of potential helical peptide inhibitor designs. We brought to their attention that isolated short helices are generally unstructured, therefore, to stabilize a helix in any inhibitors they designed, they would need to augment their plans. We provided the students a resource from the literature (Guarracino et al., 2011) where numerous helix stabilizing techniques were employed and students who discussed or implemented one of these in their designs received a greater consideration for feasibility in their final report. To gather data and design their compounds, students had class time in virtual laboratory break out rooms on Zoom, as well as time on their own throughout the week. Conveniently, they had unrestricted access to VMD via access to the TCNJ supercomputer at home or on campus. Future iterations of this project need not be tied to Zoom (or other virtual meeting space), but can take place wherever students can access the supercomputer, on and off campus.

### *Step 3: Peer Review: "The Persuasive Pitch."*

In the second week of the project, laboratory time became a workshop for students to obtain peer feedback and revisit their work, adjusting and developing

**Table 1.** Guidelines for gathering data with the VMD project, analyzing the interface between the SARSCoV-2 Spike protein Receptor Binding Domain and the ACE2 receptor.

| Criteria to include in VMD work | Additional questions to ask/answer |
|---|---|
| Amino acid residues at the interface between ACE2 and SARS-CoV-2 Spike | • What is their polarity? (charged, polar, non-polar)<br>• Are there hydrogen bonds? Ionic bonds?<br>• Other bonding? |
| Specific secondary structures at the interface | • Which helices seem important?<br>• What residues are on these helices and play a role in bonding?<br>• Are there other secondary structures on ACE2 and/or Spike?<br>• Are they part of the interface? |
| Set a distance limit of 4 Angstroms (a cap for hydrogen bonding) around a specific amino acid or subset of amino acids you found important | • What are the main contacts? |
| Generate figures and a table summarizing your data | |
| A good inhibitor could potentially bind to SARS-CoV-2 Spike, resemble ACE2, and prevent Spike binding to ACE2, freeing ACE2 to perform its natural function | • What might an inhibitor look like if it was a peptide?<br>• Would you arrange the residues in a similar way?<br>• What might you do differently than what is found in nature? |
| Short peptides on their own (not in a protein) tend to lose their secondary structure.<br>Scientists designing peptide inhibitors often lock helices into their conformations using various methods. | Using the Helix Stabilization paper provided for reference **[REF]** how might you stabilize a peptide inhibitor design? |

The number of the Team you're Reviewing: _____

Your Team Number: _____

1. Does the other Team explain their inhibitor design clearly?

*Comments:*

2. Do they explain, clearly, why they chose the area of the protein they chose?

*Comments:*

3. Is there anything that was confusing? If so, what?

*Comments:*

4. What details were helpful, good inclusions?

*Comments:*

5. What details might help supplement their work (what should they add)?

*Comments:*

6. Are there any errors that need correcting and if so what?

*Comments:*

7. Further comments or notes.

| Evaluation | Score (Indicate one) | | |
|---|---|---|---|
| Clarity | 0 | 0.5 | 1 |
| Detail | 0 | 0.5 | 1 |
| Feasibility* | 0 | 0.5 | 1 |

* "Does it make sense?"

**Figure 2.** Workshop Peer Review Form for the VMD SARS-CoV-2 project.

it further. Each team presented a 5-8 minute "pitch" to another team (through combined breakout rooms on Zoom) to explain the focus of their designs and plans. Students were asked to be persuasive, to think of the other team as investors in their inhibitor designs, and intelligent resources in the field to give advice. Each team filled out a "workshop peer review" form (Figure 2) to provide and gather constructive advice to and from their peers regarding the clarity, detail, and feasibility of their pitch. Peer review counted for a small portion of their final project grade, with consideration made for how well they responded to peer feedback in their final written work, not the grade or critique a peer gave them.

### *Step 4: Written Proposal and Final Survey*

The project culminated in the third week, with student teams writing a proposal in a style amenable for a science-educated "non-specialist." This required students to balance inclusion of explicit details (i.e. defining VMD and what is known about the spike protein in relation to SARS coronoavirus-2 infection), yet omitting non-narrative methodology (i.e. commands or steps for VMD analysis or the definition of a peptide). Each proposal had three defined sections: Description, Methodology & Approach, and Outcomes & Value, as well as a references section (Table 2). In grading, we additionally paid attention to format, miscellaneous style and peer review evaluation (Table 2). Each team was provided a rubric (Figure 3) that clarified the assessment of these different aspects of their work. Students generated all of their own figures and graphics directly from VMD. At the completion of the project, students were asked to take a voluntary, anonymous Qualtrics survey via a link through their course website, regarding the use of VMD in their class. They received two points on their final exam (which was out of 150 points) if they completed the survey and screenshot the "submitted" screen, however their specific answers were not attributed to individuals as the survey was anonymized.

The School of Science-wide initiative to encourage faculty experimentation with student-centered, active learning pedagogies aimed at broadening participation includes IRB coverage for experimentalist faculty and other key tools designed to support pedagogical research. Student performance and other course-based data can be connected to demographics, academic and persistence data, allowing faculty to disaggregate data by, for example, prior grades, race, ethnicity, and/or gender. The Chemistry department has conducted multiple successful experiments as part of this overall effort, including a full transformation of the multi-section General Chemistry I and incorporating inclusive, active-learning strategies in Organic Chemistry and elective courses (Chan, et al., 2020).

## Results and Analysis

### *Overall Integration of Molecular Visualization into the Biochemistry Course*

Outside of those students at TCNJ that engage in biochemistry or computational chemistry research, the exposure of students to biomolecular visualization tools would ultimately occur in the Biochemistry course, or possibly other Biochemistry advanced elective courses in the curriculum. Therefore, the best approach to guarantee that all of our students are exposed to some training in biomolecular visualization is to embed exercises that use these tools into the

**Table 2.** Guidelines and criteria for the final written proposal for the SARS-CoV-2 VMD project by student teams.

| Area to be assessed | Criteria for assessment |
|---|---|
| Description | • Include the problem you are targeting<br>• Present it in the context of the field<br>• Explain the goals and objectives |
| Methodology/Approach | • What you did using VMD<br>• Include figures, images and a table (if befitting)<br>• What collected data drove your inhibitor design?<br>• What is your inhibitor design?<br>• Communicate what was done |
| Outcomes and Value | • Conclusions based on your method<br>• Broader impacts, including human health<br>• Explain why you think your inhibitor is valid<br>• What would happen next (including more computer simulations, any wet lab work, making and testing your inhibitor; can be general) |
| Format | No more than 4 pages single spaced, numbered, 1 inch margins, standard 12 point font, figures included, and a reference section not included in page count |
| Style and miscellaneous | • Mature writing and communicates details well<br>• Transitions between sections and flow<br>• Feasibility of inhibitor and persuasiveness<br>• Peer review (suggestions and how were they addressed)<br>• References |

**Category 1: Project Description (5 pts)**

| | Poorly achieves this | | Lacking some detail, but does achieve this | | Achieves all and presents it well |
|---|---|---|---|---|---|
| • Well defines problem<br>• Presented in the context of the field<br>• Explains the specific goals and objectives | 1 | 2 | 3 | 4 | 5 |

**Category 2: Methodology/approach (5 pts)**

| | Poorly achieves this | | Lacking some detail, but does achieve this | | Achieves all and presents it well |
|---|---|---|---|---|---|
| • VMD methodology used<br>• Clear communication of what was performed<br>• Inhibitor design origins<br>• The inclusion of figures is purposeful and illustrative | 1 | 2 | 3 | 4 | 5 |

**Category 3: Outcomes and value (5 pts)**

| | Poorly achieves this | | Lacking some detail, but does achieve this | | Achieves all and presents it well |
|---|---|---|---|---|---|
| • Conclusions<br>• Broader Impacts<br>• Validity of inhibitor design<br>• Future directions | 1 | 2 | 3 | 4 | 5 |

**Category 4: Style and other (5 pts)**

| | Poorly achieves this | | Lacking some detail, but does achieve this | | Achieves all and presents it well |
|---|---|---|---|---|---|
| • Mature writing with clear, detailed communication<br>• Feasibility of inhibitor<br>• Peer Review<br>• References | 1 | 2 | 3 | 4 | 5 |

**Figure 3.** Rubric for final written proposal for the VMD SARS-CoV-2 project.

required Biochemistry course in our curriculum. By providing students with a background in molecular visualization, they are exposed to some of the computational tools used by chemists in both academia and industry. As a result they are more prepared to understand how visualization can be used in combination with other experimental methods to better understand biomolecular systems.

### Outcomes from Use of the VMD Tutorial

The specific goals of the VMD tutorial that we introduce the students to in class include (1) understanding what experimental methods are used to derive the structures that are included in the Protein Data Bank (PDB), (2) understanding how to interpret the information contained in a PDB file and to find additional information about the protein that is curated on the PDB information page for a particular accession code, (3) learning how to obtain a PDB file from the Protein Data Bank, and finally (4) learning how to load a PDB file into the VMD software and perform basic manipulations and analyses on the molecule (e.g., changing the graphical representations for the molecule, creating selections for specific groups of atoms or amino acids in the molecule, measuring distances between atoms, and measuring secondary structure content of a protein). These are some of the most common tasks that would provide transferable skills to students going forward to other classes/research at the undergraduate level, or upon moving on to postgraduate studies or industry. Therefore, these were the main points we focused on for this introductory VMD tutorial.

Biochemistry students across the years responded positively to the training module each time it was incorporated into class. The VMD tutorial was used in 2017, 2018 and 2021 in our one-semester biochemistry classes and in 2020 in a special topics in biochemistry class (with a similar population of students; chemistry majors, juniors and seniors). Overall, student performance on the initial tutorial has been consistent, even with minor changes to the specific content (Table 3). Moreover, performance on the tutorial was in line with (if not greater than) overall performance on the laboratory portion of the course, indicating that the assignment was reasonable and that students showed steady comprehension of the materials over time (Table 3). While the details of the module itself may change (i.e. different protein interactions observed), the type of measurements and guided questions they encounter has remained consistent, and student evaluation is reliable as it follows a set criteria for students to use when answering specific questions. While it has thus far been adopted by one instructor for biochemistry, the parameters and evaluation materials are well-defined and generalized allowing for greater adoption by other classes. An example of the VMD training assignment can be found in the *supplementary materials*.

### Outcomes from Using VMD on the SARS-CoV-2 Spike Protein-Receptor Project

When students began the SARS-CoV-2 VMD project in Spring 2021, they had just completed the tutorial the week prior. Performance on the final proposal averaged an 89.4, which was commiserate with their work on the tutorial and their overall lab grades. This indicated that the assignment fit well within the accepted trajectory of knowledge building throughout the lab portion of the course, and that the work was appropriate within standard student progress. For reliability in this first iteration of the project, one instructor graded the proposals. The explicitly-defined rubric (Figure 3), distributed to the class prior to their writing, was used for evaluation and students were assessed on four general criteria.

Of these criteria, the "conclusions" and their "discussion of broader impacts" as well as the "validity of their inhibitor" were their highest scoring sections, with an average of 4.96 out of 5. As the assignment made them examine the biochemistry of a real-world phenomenon of great importance, understanding the impact of their undertaking, and subsequent reflection on their work clearly resonated with the students. This particular portion of the proposal had students place their work in a larger context and helped them

**Table 3.** Student outcomes on the VMD tutorial over several years in comparison with overall lab grade for course.

| Term/Year | Number of Students | Grade on tutorial (out of 10) | Lab average for course |
|---|---|---|---|
| 2017 Spring (in-person) | 28 | 8.6 | 83.8 |
| 2018 Spring (in-person) | 31 | 9.1 | 86.8 |
| 2020* Spring (shifted remote) | 8 | 9.5 | 85.8 |
| 2021 Spring (remote) | 26 | 8.9 | 89.6 |

*This semester was a Special Topics in Biochemistry course which students took concurrently or after they had taken the Biochemistry course, and shifted to remote instruction during the pandemic.

make the connections between the contents of their learning and its importance. However, the weakest area of the proposals, with an average of 3.75 out of 5, was the "discussion of the methodology using VMD" and "communication of their results and designs." While all groups contributed figures obtained from their VMD usage, the purposeful inclusion of specific figures to illustrate the details of their study was lacking in several cases. In the future, having an additional week for students to become acclimated to the software as well as iterative peer review and a longer time with further guidance for designing inhibitors can aid student comprehension of the methods and their proper use.

The resultant student work revealed their mastery and depth to their biochemical knowledge (Figure 4). Students measured the distances between amino acid residues on the SARS-CoV-2 spike protein receptor binding domain and the ACE2 receptor that interact via hydrogen bonds and electrostatic interactions. From here, they described the residues close enough for such interactions to determine which might be most important. Some students included a brief discussion of which residues, of the ones they chose,

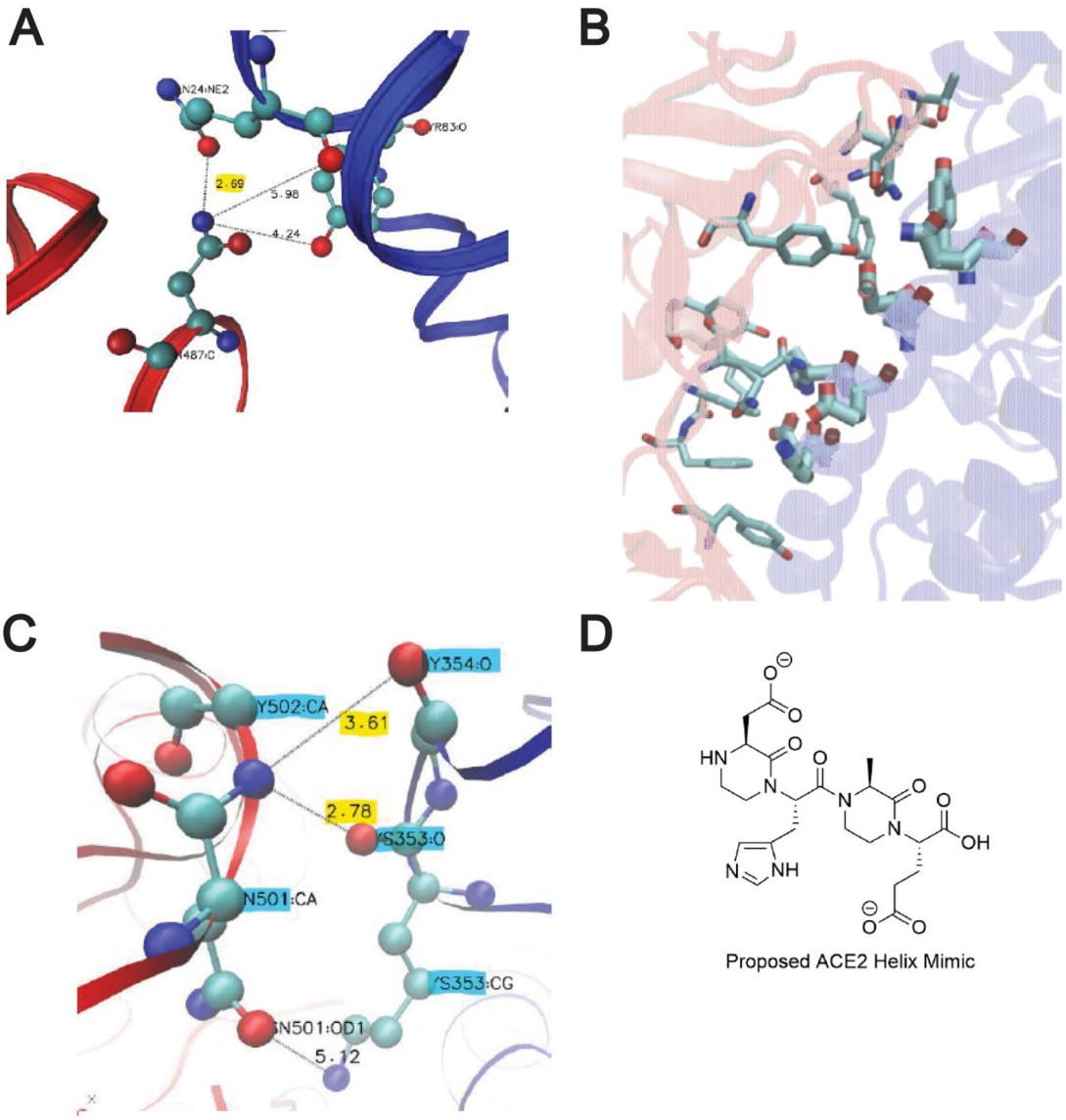


**Figure 4.** Representative Student Work (Lan et al., 2020, Guarracino et al, 2011) A. Students measured the distances between the SARS-CoV-2 spike protein receptor binding domain (RBD) and the ACE2 receptor that interact via hydrogen bonds and electrostatic interactions. B. Students visualized the specific residues that were close enough between the spike protein RBD and the ACE2 receptor C. When measuring specific distances for electrostatic interaction, students proposed amino acid substitutions that could be incorporated into an inhibitor. D. Students used a class of helix mimetic, oligooxopiperizine, as a stabilizing design for their inhibitor.

differed from the first SARS coronavirus from 2002, SARS-CoV-1 (Figure 4A, B). When developing their own plans for peptidomimetic inhibitors, some groups focused on the residues important for the alpha helical interface, designing a mimetic that resembled part of the ACE2 receptor. Others proposed thoughtful amino acid substitutions in their inhibitors, such as changing a lysine to a histidine with a similar charge but different length and shape, to aid binding (Figure 4C). In some cases, students pulled from their research experiences and the primary literature and designed non-natural peptide mimetics that would display the amino acid side chains in a way to emulate the natural system best (Figure 4D). The inhibitors designed were interesting, many were feasible, and furthermore, this project provided a springboard for student innovation, sparking creativity in student research planning and thinking about connections between biochemistry and medicine.

### Outcomes from Student Survey Information: student Perceptions

We assessed student perceptions of their comprehension, confidence and interest in using VMD as a tool for studying biochemistry. Twenty-two out of twenty-six students in the Spring 2021 biochemistry class cohort answered the survey at the close of the semester. While the sample size of students assessed is low, as this was the first iteration of this particular project, some valuable information can be gleaned from their responses.

The molecular visualization students perform in Biochemistry is part of a larger group of activities in molecular modeling and visualization that have been embedded across our undergraduate Chemistry curriculum. For example, computational chemistry modules have been implemented in our General Chemistry, Organic Chemistry, Quantum Chemistry, and Chemical Thermodynamics courses as well. This effort to integrate computation across our curriculum exposes students to the idea that computation and visualization is an integral and central part of chemistry, and that it is of paramount importance that students become familiar with computational chemistry tools as they enter a modern chemistry workforce that is increasingly driven by computing and data science. As students typically take Biochemistry later in their course sequence, these earlier experiences in computer modeling and visualization provide students with a general foundation for the use of such techniques. Herewe provide some data from a recent survey of General Chemistry students who performed molecular visualization of small molecules using the online cloud-based computational chemistry platform Envision (Entos, 2021). This important example demonstrates how integral chemical visualization is to students across the chemistry disciplines and beginning with their first chemistry classes. In particular, in the Fall 2021 semester this module was used across all of our General Chemistry students, which led to a sample size of 251 students. One of the main findings from our survey was that 217/251 either agreed or strongly agreed that using molecular modeling software to help them visualize molecules helped them to understand the 3-dimensional shapes of molecules better than static textbook images alone. This was reiterated by students in the biochemistry class undertaking the project described in this manuscript. Students also responded favorably that they would use the Envision software again on their own to visualize molecules (3.82 +/- 1.23 on a 0 to 5 scale), and that they would like to see Envision or other molecular modeling tools used in other Chemistry courses (4.07 +/- 1.05 on a 0 to 5 scale). These types of positive responses from students about molecular visualization are what have encouraged us to continue to embed computational tools into our curriculum, and the results we see with first year General Chemistry students are consistent with those we have observed with Biochemistry students using VMD as discussed below.

### Survey of VMD Tutorial Perceptions from 2021

As the students enrolled in the biochemistry course are primarily juniors and seniors, many would have seen computational chemistry tools in General Chemistry and Organic Chemistry. However only students in a computational chemistry research group would have previously used VMD. Specifically, 17/22 students responded that this exercise was the first time they had ever logged into the TCNJ supercomputer, and 18/22 students responded that it was their first time ever using VMD. Additionally, only 3/22 students had ever accessed the Protein Data Bank prior to this activity. Students responded very positively to the use of VMD as an aid for better visualization of biomolecules compared to 2D images (9.00 +/- 1.58 on a 0 to 10 scale) with 20/22 students selecting an 8 or higher for this question. Students were also asked whether they would use VMD again for tasks that require biomolecular visualization (e.g., coursework, research, job-related, etc.). Here students also responded positively with a mean and standard deviation of 7.86 +/- 1.94. From

our perspective this is a very positive response, and it is likely that with more opportunities to use the software that students would become increasingly comfortable in using it for other tasks. Importantly, as discussed below, 20/22 students responded they agreed with the statement that the VMD project involving the spike protein and the ACE2 receptor was helpful to their overall learning (the remaining 2 responses chose the neutral response, instead of disagreeing with the statement). This suggests that there is great enthusiasm from students to utilize computational tools to better understand chemical systems. The integration of computational skills across the curriculum at TCNJ is an important aspect of the continuing modernization of our courses.

### *Survey of VMD SARS-CoV-2 Project Perceptions*

When asked about applying their newly acquired skills using VMD on a new project students could choose as many qualifiers from a list as they wished and/or could add their own under "other." Figure 5A shows the responses; students mostly found the experience to be a good one that was also challenging. It is clear that using the hands-on approach to visualization improved student interest in viewing biological molecules. Evidence of this is shown by the largely increasing number of students with average to high interest in biomolecule visualization (Figure 5B). Using projects, like this one, as a tool to build students' comfort levels with new skills is beneficial to the subject matter at hand and future coursework and research. We assessed student confidence levels using the VMD software prior to and after the application-based project, with the majority of students switching from low confidence to average to high confidence (Figure 5C). Overall, 91% of the students (20 of those who answered the survey) agreed that the project was helpful to their overall learning in the class, with 9% (2 students) neither agreeing or disagreeing (Figure 5D). This provided overwhelming evidence that the project was supportive to biochemistry learning.

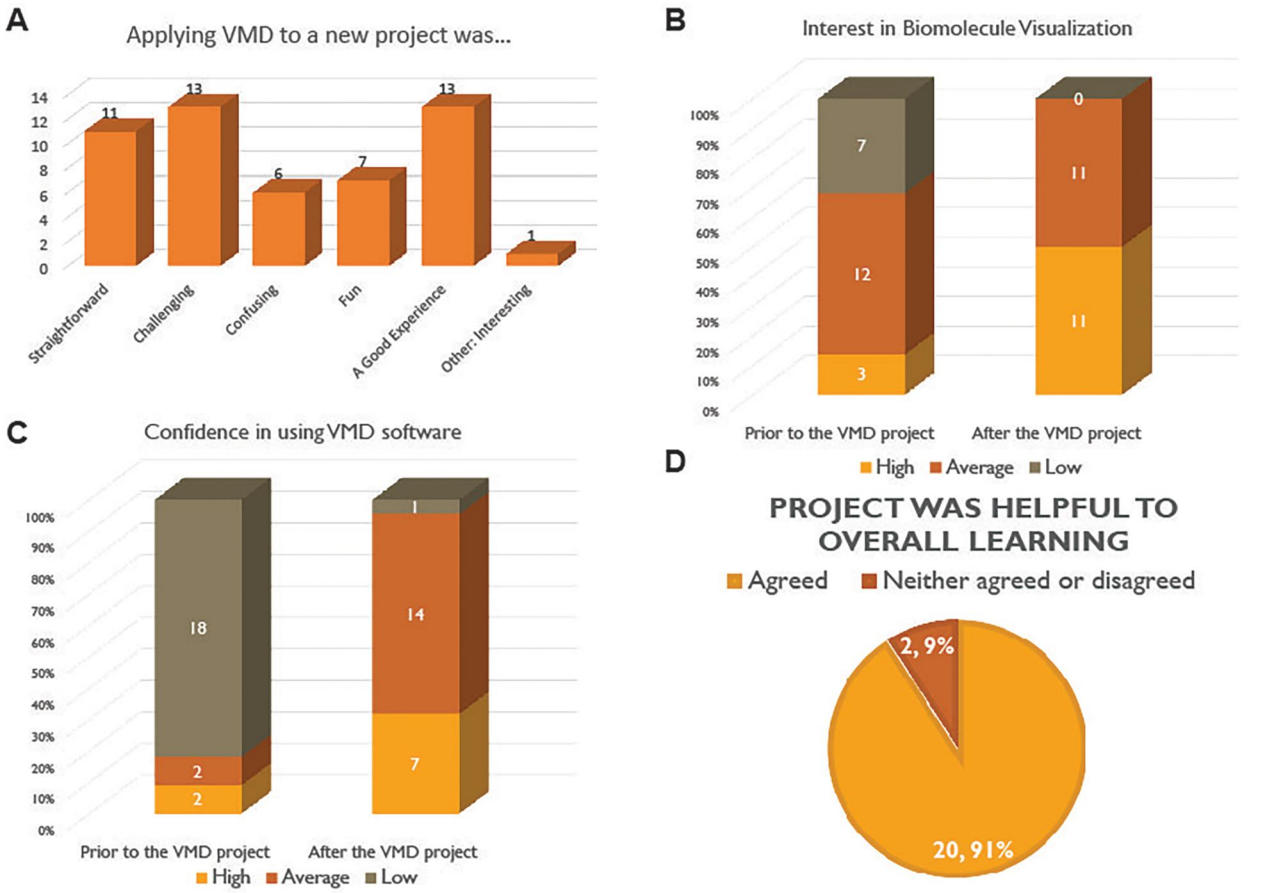


**Figure 5.** A. Student perception of their application of the newly acquired skills. The qualifiers listed were provided, and "other" represents a space for them to write in their thoughts. B. Gauging student interest in biomolecule visualization prior to and after the VMD project C. Gauging student confidence levels in their application of the software prior to and after the VMD project. D. Overall student perception of the project as helpful to their overall learning in the class.

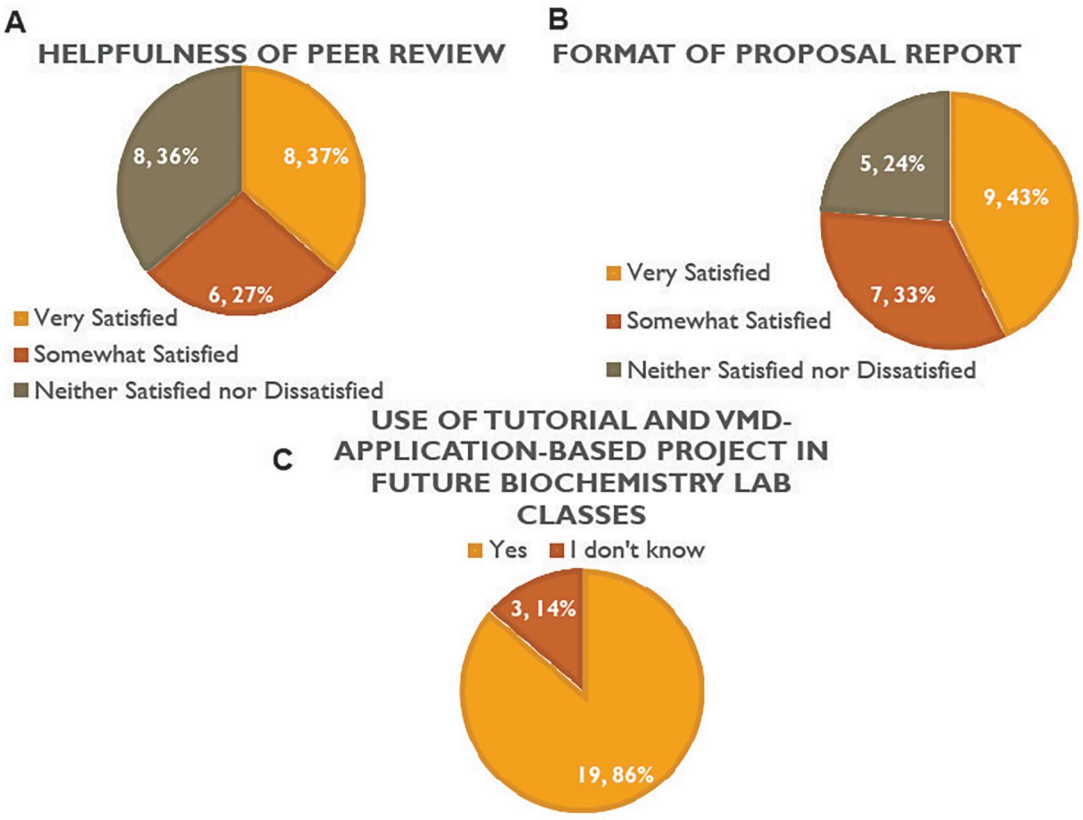


**Figure 6.** A. Student satisfaction with the helpfulness of peer review. B. Student satisfaction with the format of the final proposal report. C. Student suggestion regarding use of the tutorial and VMD application-based project in future biochemistry classes.

We further assessed the students' thoughts about specific aspects of the project. Regarding the helpfulness of peer review, a majority of students expressed they were satisfied to some level with the process (Figure 6A). The use of peer review was valuable to the students' progress through the project, as interpreted by this collected information. However, future changes to the manner, duration and usage of peer review can help support this integral part. Working together over a longer period of time and extending the evaluation feedback (Figure 2) to include more specifics could help bolster this aspect. When evaluating the format of the written proposal, again the majority of students expressed some level of satisfaction (Figure 6B). To add value to the exercise, future versions of the project can have students model this style of report for other labs throughout the semester to increase their comfort with the format and repetition through the course. A workshop that involves writing in this style and/or feedback on an earlier draft could also be provided.

### *Survey of VMD Usage across the Tutorial and Project*

Ultimately, the students were asked if they thought the VMD tutorial and application-based project would be useful additions to future biochemistry labs, regardless of class format (including remote, in-person, hybrid etc.). An incredible 86% (19 students) replied "yes," with 3 students (14%) stating "I don't know" (Figure 6C). While many students provided open-ended comments regarding their favorite and least favorite aspects of the project, there were a few notable and relatable comments that can help guide the development of the project in the future. Most of the favorite aspects revolved around the real-world application of the project. One student commented that they truly appreciated "being able to see the two structures and analyze the parts of the proteins that caused all the chaos in the world." Another mentioned how "the visualization aspect and being able to closely relate it back to my coursework [was their favorite part]. When I finished my assignment I felt like I understood the protein complex so much better!" In both instances, and others not included here, the student consensus showed that a combination of hands-on experience in manipulating a three dimensional image of a protein combined with the real-world application of such imagery were the most favorable aspects of the work. Least favorite included confusion upon "trying to get used to the system," that "reading the data provided took practice" and the inherent frustration "getting stuck in VMD

when I wanted to do something but didn't know how to do it." To expect rapid skill utilization is a sizable challenge given the short amount of time the students spent training to use the software. In the future, more structured one-on-one input and remediation as the students train could increase their familiarity and provide troubleshooting on an individual basis.

### Course Demographics and Implications to Pedagogy

Demographically, this section of Biochemistry was fairly evenly split between men (46%) and women (54%). The racial and ethnic make-up of the class (Asian: 31%, Black: 8%, Latinx/Hispanic: 23%, White: 31%, Other: 8%) reflects the overall distribution of the School of Science. Although the course size is too small to establish statistical significance across demographic groups (n = 26), we note some encouraging trends. Nearly all students passed the course successfully (96%). Half of students from minoritized groups in higher education (BIPOC, men) earned grades at or above their cumulative GPA, while White students (25%) and women (36%) were less likely to achieve a grade at or above their overall GPA. This suggests that the student-centered, inclusive pedagogies employed in this course do, in fact, benefit historically marginalized students when compared to other courses.

Our results reflect broader trends within our efforts to incorporate visualization techniques and other skills using active learning pedagogies shown to support all students. General Chemistry I, where visualization skills are introduced, serves a much larger population of students (n = 266 across all Fall '21 sections), which allows for significance tests. Compared to biochemistry, the course had a similar make-up by gender (56% women/44% men). However, the racial and ethnic make-up skewed more toward White (51.5%) and Asian (18.4%). Minoritized groups including Black/African American (5.6%), Hispanic/Latinx (15.4%), and multi-racial (3.8%) made up a much smaller proportion than in biochemistry. Mean grades for women (3.22, ~B) were higher than for men (mean = 2.89, ~B-), (p=.01). Significant differences (p=.03) also appear across racial and ethnic groups, with mean grades for Asian (3.37, ~B+) and White (3.11, ~B) students higher than for African American/Black (2.7, ~B-) and Hispanic/Latinx (2.79, ~B-) students. While this grade distribution reflects underlying structural inequality in the K-12 school system, we are encouraged that across all groups more students receive a grade equal to or higher than their cumulative GPA, without significant differences by race. This suggests that these active learning course designs move us toward achieving our inclusion goals.

### Using VMD and Its Applications in Science Literacy

Science education goes beyond teaching the next generation the basic knowledge of scientific facts, but has students build a familiarity with the processes and practices of science, from its personal applications to those that affect civic decisions at the community level (Holbrook & Rannikmae, 2009, Koballa et al., 1997). As we have seen with the COVID-19 pandemic, making 'sense' of science is necessary to achieve larger range societal goals and can be impaired by mis-information or a lack of understanding. This has been the case for many hotly debated topics such as vaccines, climate change, genetically modified foods, and stem cell research, to name a few (Impey et al., 2011). Science educators are tasked with bolstering student skill levels, maintaining student trust in science, as well as complementing individual student identities and worldviews. Through the lens of scientific literacy, the use of molecular modeling software can be a great asset. Students of all levels often have trouble visualizing three dimensional molecules when looking at them for the first time, especially as a flat two dimensional picture. When those same molecules bear importance to the "real world"—perhaps a protein involved in cancer, or a stretch of therapeutic RNA—the stakes of understanding are higher, but student interest levels also increase. Often students are overwhelmed trying to rectify the materials they learn with the applications they may hear about in the news or even a popular science website. Being able to properly visualize these molecules, to rotate and manipulate them in ways that are conducive to their use, can enhance understanding, diminish fear, and help these students when faced with scientific decision-making. From designing new therapies to voting on policy changes to enforce or regulate certain substances, scientific literacy is at the helm of progress. The application of visualization techniques can bridge the understanding-gap while making scientific exploration fun.

## Conclusions

Broadly, the project described could be used in future biochemistry classes, and other molecular medicine-related courses. Each team of students could examine a different protein-protein interaction involved in disease, be given adequate time to train and practice the VMD techniques, and ultimately present more formal pitches to each other as part of the full proposal. While different teams may not know the specifics of

another team's molecules, the groups can debate their designs, efficacy, or how they might vote for the use of a different team's inhibitor, based on the thoroughness by which they communicated with each other. As described above, the molecular visualization component of this project also provides students with a broadly transferable skillset. In the Biochemistry course students build upon previous experiences using different modeling tools in courses like General Chemistry, Organic Chemistry, and others, to examine small molecules, and extend this knowledge to learn the new visualization tool, VMD, to explore biomolecules. These experiences help to prepare students to enter modern academic and industrial environments which are increasingly integrating computational tools into all aspects of science and engineering workflows. Using visualization software to aid the study of biological molecules and structuring projects for open-ended student inquiry creates a space for students to expand their biochemical learning while engaging actively in the process. When students have agency over their outcomes, use their creativity, work together, listen to each other, and teach each other about an important subject in science, they are modeling science literate behavior while learning new materials. It is our hope they will take this with them outside of the classroom and that projects such as the one described here will provide a memorable springboard for their continued paths in and out of science.

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